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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/927,790	08/10/2001	Bassil I Dahiyat	A-67229-9/RFT/RMS/RMK	6955

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EXAMINER

BORIN, MICHAEL L

ART UNIT PAPER NUMBER

1631

DATE MAILED: 01/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/927,790

Applicant(s)

DAHIYAT ET AL.

Examiner

Michael Borin

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on 13 October 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 33-45 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 33-45 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

DETAILED ACTION

Status of Claims

1. The Examiner acknowledges amendment filed 10/13/2005 presenting new corrected set of claims.

Claims 33-45 are pending.

2. A request for continued examination under 37 CFR 1.114 was filed in this application after final rejection. This is the first Office action after the finality of the previous Office action of 04/21/2004 has been withdrawn.

Claim Rejections - 35 USC § 112, second paragraph.

The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claim rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The rejection is applied for the following reasons.

It is not clear what constitutes "primary variant positions" in claim 33, step c) , the specification does not define this term, and it is not clear which positions are considered as "primary variant positions", from which sequences they are obtained, and how the list of such positions is generated. Further, is the list of positions lists their location (e.g., residue #1, residue#2, etc), or their nature (e.g., Ala, Val, ets). If the former is correct, than it is not clear how, in step d), sequences are generated from the

numerical identifiers of amino acid residues. Note that specification addresses “positions” and amino acid residues in the alternative:

... variant positions and/or amino acid residues in the variant positions

See specification, paragraph [0108].

Claim Rejections - 35 U.S.C. § 101/ 112-1

4. Claims 33-40 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific asserted utility or a well established utility.

The rejection is maintained for the reasons of record – see the original rejection in the Office action of 02/19/2003, and extensive responses to arguments in the Office actions of 09/26/2003 and 04/21/2004 – and further in view of the following.

Examiner maintains that the instantly claimed method provide for generating a secondary library of as yet undetermined structure, function or biological significance which is obtained by a random combination of amino acid residues derived from a plurality of variant positions. Note that specification, paragraph [0108], guides that that ... in general, the variant positions and/or amino acid residues in the variant positions can be recombined in any number of ways to form a new library that exploits the sequence variations found in the primary library.

There is no evidence of record or any line of reasoning that would support a conclusion that the secondary library was, as of the filing date, useful for any industrial or any pharmacological uses. Until some actual and specific significance can be attributed to the secondary library or even the compounds present the library, an artisan

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would be required to perform additional experimentation in order to determine how to use the generated secondary library. Thus, there was no immediate "real world " utility as of the filing date. Because any potential pharmacological utility is not yet known and has not yet been disclosed, the utility is not substantial because it is not currently available in any specific and practical form. The specification does not disclose substantial interpretation for the result; and none is known in the art. In order for generated library to be useful, as asserted, for any pharmacological use, there must be a well- established or disclosed claimed library correlation or relationship between the and a disease or disorder. The secondary library of as yet undefined structure allegedly generated from the claimed method does not have a specific and substantial or real-world utility well-established utility.

For example, for a protein having 100 residues, and assuming that all 100 positions are considered to be "variant positions" and the residues are natural amino acids, the secondary library will be comprised of a random permutation of all 20 natural amino acid residues. Utility of such random library is not addressed neither in specification, nor in applicant's response. The above considerations addresses applicant's request to demonstrate why one of ordinary skill in the art would question the asserted utility of the invention.

Further, note that prior art acknowledges that design of proteins is largely unsuccessful. See, e.g., Shakhnovitch (Folding and Design, 1998, 3, R45-R58):

"Most of the present experimental [protein design] approaches enjoyed only limited success, providing polypeptides that in most cases fold into compact but mostly disordered conformations of molten-globule-like species. It is quite possible that limitations in experimental design result from a relatively low synergism between experiment and theory." p. R45, right column.

Applicant repeatedly addresses article of DeGrado and asserts that DeGrado demonstrates the utility of the instant method. However, the statements of DeGrado, such as

Dehiyat and Mayo describe a new approach that makes de novo protein design as easy as running a computer

does not address neither the merits of the particular method as instantly claimed, nor suggests a specific or substantial utility for a "secondary library" generated by the instant method.

Further, citation of DeGrado

They have distilled the rules, insights and paradigms gleaned from two decades of experiments into a single computational algorithm

does not relate to the instant specification which clearly lacks a "single computational algorithm" but rather offers a plurality of permutations of various computational steps, out of which the instant claims present one particular combination of such steps.

With respect to Saven publication, which as applicant acknowledges is not a prior art, Saven does not address the instant method, and rather addresses general state of art at post-filing time.

5. Claims 33-40 are also rejected under U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific asserted

utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claim Rejections - 35 USC § 102 and 103.

6. Claims 33-40 are rejected under 35 U.S.C. 103(a) as obvious over Topham et al.

The instant claims are drawn to a computational method to generate a library of protein variants (secondary library) comprising:

- a) inputting coordinates of target protein into computer;
- b) generating a set of primary variant sequences utilizing a scoring function;
- c) generating a list of primary variant positions in said primary variant sequences;
- d) combining a plurality of said of primary variant positions to generate a secondary library of secondary sequences,
- e) synthesizing a plurality of secondary sequences

Topham et al teach method of modeling protein variants including the steps of generating library of sequences using an alignment program (i.e., a set of primary variant sequences; see abstract, p. 195, last paragraph, p. 196, section (a) and last paragraph); selecting variant positions for which frequencies of residue type occurrence (N_{freq}) and probability distribution of variant amino acid residues is determined, and thus generating secondary library.

Topham does not teach synthesizing the sequences of the secondary library, particularly with the steps of claims 34-40. It would be obvious to one skilled in the art, however, that the desirable end stage of any protein modeling is synthesis of proteins of interest. Further, selection of PCR method to synthesize proteins would be obvious to an artisan as it is one of the main methods of protein synthesis, and selection of particular parameters of PCR would be obvious to an artisan as a part of routine selection of optimal parameters.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Borin whose telephone number is (571) 272-0713. The examiner can normally be reached on 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, Ph.D., can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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A handwritten signature in black ink, appearing to read 'Michael Borin', with a long, sweeping horizontal stroke extending to the right.

Michael Borin, Ph.D.
Primary Examiner
Art Unit 1631

mlb
01/13/2006